

# Neuropsychological Assessment for Detecting Adverse Effects of Volatile Organic Compounds on the Central Nervous System

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Because there are no direct biological markers for the substances implicated in indoor air exposure, it is impossible to directly measure if an individual or group of individuals has been exposed to a potentially neurotoxic substance in the workplace. Behavioral changes may be the earliest and only manifestation of central nervous system (CNS) effects and are often too subtle to be revealed by routine physical or neurological examination. Neuropsychological techniques are sensitive to subtle behavioral/cognitive changes that can result from exposure to neurotoxins. These techniques consist of oral and written tests that are administered by a trained examiner on a one-to-one basis. In general, a wide variety of cognitive domains are evaluated. The typical battery generally includes assessing orientation, attention, intelligence, language, visual memory, verbal memory, perception, visuoconstruction, simple motor speed, psychomotor speed, and mood. As with most assessment techniques, the neuropsychological methods have limitations. One major drawback is the availability of appropriate norms that are used to compare the results of a specific individual. Because these tasks are greatly affected by age, intelligence, and in some instances sex, the availability of appropriate norms is mandatory to determine if the CNS has been effected.

Although neuropsychological tests are sensitive to the presence of CNS involvement, they are not specific. Patterns of performance seen with specific instances of neurotoxic exposure may also be seen with a number of other diseases of the CNS such as dementia, cerebrovascular disease, hydrocephalus, or normal aging. In addition, neuropsychiatric symptoms such as anxiety and/or depression are often manifested as cognitive difficulties that will mimic the cognitive dysfunction seen with toxicity of the CNS. Some of the more sensitive neuropsychological tests are presented. Interpretations of test performance as they relate to toxic effects on the CNS are discussed.

## Introduction

Substances that have been reported to cause changes in mood and behavior with low-level exposure include lead, mercury, manganese, carbon disulfide, methylbromide, pentaborane, ethylene glycol monoethyl ether, and narcotic solvents (1). The patient may complain of vague central nervous system (CNS) symptoms before any clear-cut CNS changes can be measured. In patients with known neurotoxic exposures, clinical complaints include inability to concentrate, loss of memory, depressed mood, anxiety, restlessness, loss of interest in work, changes in libido, general apathy, confusion, sleep disturbance ranging from insomnia to somnambulism, irritability, headaches, and weakness.

Unfortunately, biological markers for solvents that compose volatile organic compounds (VOC) in indoor air are difficult to measure because of their rapid metabolism and clearance. Because solvents are known to cause behavioral changes as a result of adverse effects on the nervous system, it has also been speculated that VOCs have a negative effect on the CNS. Because

these behavioral changes are often too subtle to be revealed by routine physical or neurological examination, the measurement of cognitive ability using neuropsychological techniques provides a method, albeit indirect, for evaluating the integrity of the CNS.

## Neuropsychological Effects

Abnormal neuropsychological results reflect CNS involvement. If CNS dysfunction exists, specific patterns of performance provide additional information about the nature of brain injury. These performance patterns will show if neuropathology is static or progressive, acute or chronic, diffuse or localized. If performance deteriorates after the individual is removed from the source of exposure, this indicates a progressive disease process that is uncharacteristic of solvent/VOC exposure. When results show a decline in a specific cognitive domain such as memory, which is inconsistent with the individual's general level of intelligence as determined by either test results, school records, or occupational achievement, then an acute process is likely and would be consistent with neurotoxic effects. Specific patterns of performance are examined to determine if brain injury is diffuse or localized. If findings are localizable, then a diagnosis of neurotoxic exposure to solvents/VOCs is unlikely and an EEG and CT/MRI are indicated.

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## Neuropsychological Techniques

Historically, neuropsychological techniques have consisted of oral and written tests that are administered by a trained examiner on a one-to-one basis. Recently, a number of computerized test batteries have also been developed [i.e., the World Health Organization Neurobehavioral Test Battery and the Neurobehavioral Evaluation System-NES-2 (2)]. Advantages and disadvantages exist for both interviewer-administered and computer-administered tests. For interviewer-administered tests, the advantages include human interaction and encouragement by the examiner, the ability to determine problem-solving strategies by actually observing the individual perform the tests, and the ability to administer tasks requiring verbal presentation and verbal responses. For example, verbal memory cannot be adequately assessed by a computer without sophisticated computer hardware. The disadvantages of interviewer-administered tests include standardization of administration between different testers and between testing sessions. In epidemiological investigations, interviewer-administered tests are more labor intensive and require a large study team to administer the tests.

Computerized testing offers excellent standardization in administering and scoring these tests. Furthermore, in epidemiological studies, multiple work stations and computers can be set up to test groups of workers simultaneously. However, normative populations are not available for computer-administered tests, which is not the case for interviewer-administered tests. The normative values for interviewer-administered tests cannot be used to compare the results of written tests adapted for the computer because the performance demands of the tasks change even though the tests appear to be similar.

The cognitive domains, which are generally evaluated in any neuropsychological evaluation, are presented in Table 1. There are many well-standardized neuropsychological tests that can evaluate each of these cognitive domains. Lezak (3) describes most of the available tests and is an excellent reference source. The tests that will now be described have been chosen because they have proven to be useful in evaluating neurotoxic effects.

Orientation is generally evaluated by asking about person, place, and time or by a brief mental status examination such as the Mini-Mental State Exam (MMSE) (4). The MMSE was designed to detect dementia and delirium. Because the MMSE fails to detect impairment in approximately 50% of cases with either right hemisphere or diffuse brain damage (5), symptoms associated with neurotoxic exposure are often too subtle and too diffuse to be detected by this instrument.

### Verbal Intelligence Assessment

Verbal intelligence can be assessed using the Verbal Subtests from the Wechsler Adult Intelligence Scales (WAIS-R) (6). For brevity of testing, the vocabulary subtest can be used alone to obtain a good estimate of verbal intelligence because it correlates ( $r = 0.82$ ) with the full-scale intelligence score (6). On this test, definitions of vocabulary words presented orally by the examiner are required. The responses are scored by strict criteria. The time of administration is approximately 10 min. Performance on this test is very resistant to any CNS injury. Even in cases of probable senile dementia of the Alzheimer's type, performance is gen-

Table 1. Cognitive domains assessed

Orientation
Verbal intelligence
Language
Remote
Memory
Anterograde memory
Verbal
Visual
Visuoception/visuoconstruction
Executive/motor
Depression/anxiety

erally congruent with the person's premorbid level of intellectual functioning. In addition, this test is a better estimation of intelligence than level of education (7). In past eras, higher levels of education were the exception, rather than the rule, especially in women. Because verbal intelligence will affect performance on the majority of neuropsychological tests, it is necessary to predict the level at which someone is expected to perform. When performance in a specific cognitive domain (memory, for example) falls below level of intelligence, then a cognitive decline from baseline is indicated. When exposed versus unexposed groups are equated for intelligence in epidemiologic investigations, the vocabulary test has proven to be an excellent tool to measure general level of intelligence without having to administer an entire WAIS-R, which can require 1 to 1.5 hr to administer.

Another test that correlates highly with the vocabulary test ( $r = 0.74$ ) and is also resistant to CNS impairment is the similarities test from the WAIS-R (6). As the name implies, the formulation and expression of the similarity between objects and/or concepts such as the relationship between an orange and a banana is required.

Although there are many standardized tests to evaluate language and aphasia, such as the Western Aphasia Battery (8) and the Boston Diagnostic Aphasia Battery (9), extensive evaluation of this cognitive domain in suspected cases of neurotoxic exposure is unnecessary because most neurotoxins do not selectively impair language. However, if deficits in language are found (i.e., paraphasias), then an alternative etiology for symptoms is suggested. The significant aspects of language can be quickly assessed by confrontational naming, repetition of words and phrases, spontaneous writing of a sentence, writing a sentence to dictation, and rating verbal expression.

At low levels, neurotoxins affect new learning and recent memory, and they do not affect remote memory. If gaps exist in the individual's early memories, then a neurotoxic etiology is unlikely. Remote memory can be assessed by asking about significant early life events (wedding or occupational details, etc.).

Difficulties with anterograde memory (ability to learn new information) is one of the characteristics of neurotoxic exposure. Therefore, it is important to evaluate this cognitive domain thoroughly. The Rey Auditory Verbal Learning Test (RAVLT) (10) requires memorization of a list of 15 words that is presented orally by the tester. Since the entire list of words is administered a total of five times, measurements of immediate memory (performance on the first trial) and the ability to benefit from repetition of material or total recall (performance on trial 5) are provided.

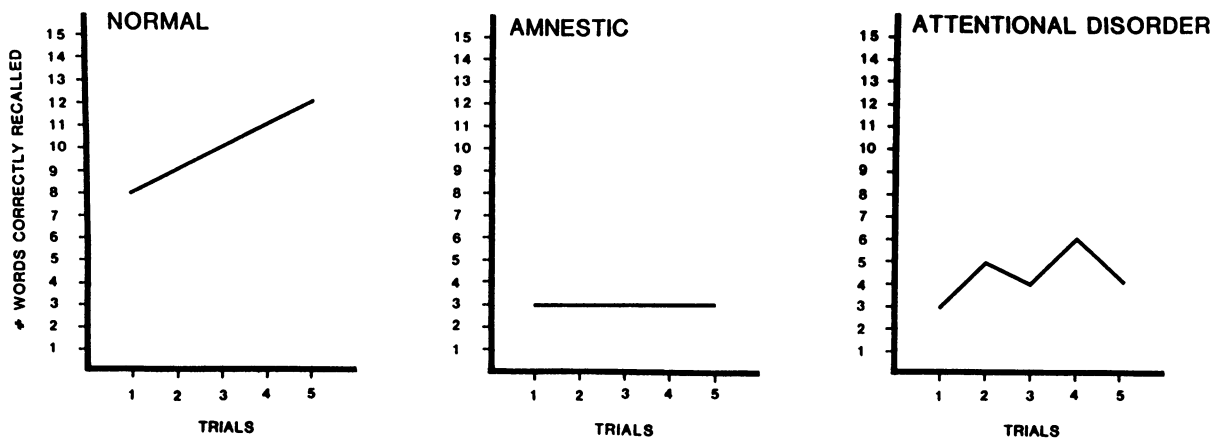


FIGURE 1. Learning curves on the Rey Auditory Verbal Learning Test in different populations.

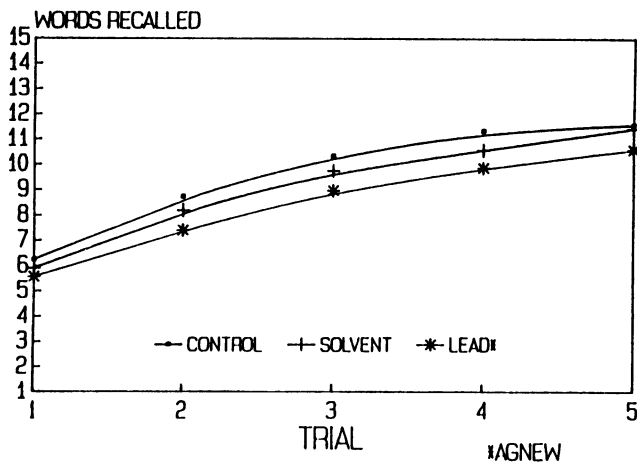


FIGURE 2. Learning curves on the Rey Auditory Verbal Learning Test in controls, lead workers, and solvent workers.

Figure 1 shows common learning curves (performance over trials) in a control group, patients with memory disorders (amnestics), and individuals with attention disorders. Patients with a disease like Alzheimer's disease and Wernicke-Korsakoff syndrome would be included in the amnesic group. Attention disorders are generally associated with either subcortical damage or psychiatric illnesses such as anxiety, depression, or psychosis. The characteristic pattern of performance in neurotoxic exposure is preservation of learning but at a lower level than normal. This is illustrated in groups of lead and solvent exposed workers in Figure 2.

Retention of information is assessed by delayed recall, where the list of 15 words is recalled after a 30-min period. Forgetting more than three words when compared to trial 5 recall is considered abnormal (3). For recognition, a list of 50 words including the original 15 words is presented, and the originally presented 15 words must be identified. Examination of performance differences between free recall on trial 5 and recognition will clarify the specific nature of the memory disturbance. For example, if eight words are recalled and eight words are recog-

nized, then the memory deficit can be attributed to acquisition difficulty. On the other hand, if eight words are recalled on trial 5 but 14 words are recognized, then recall, not acquisition, is responsible for the memory disturbance. If acquisition was impaired, more words would not be recognized than recalled because the words would not have been learned initially. Acquisition difficulties are generally seen with neurotoxic and amnesic syndromes, whereas recall difficulties are generally seen with frontal lobe and subcortical damage and psychiatric disturbances.

### Visual Memory Assessment

Visual memory can be evaluated by various methods. The individual can be required to study a drawing for a specific amount of time, and then reproduce (draw) this design from memory. The Visual Reproduction Subtest from the Wechsler Memory Scales (11) and the Benton Visual Retention Test (12) use this approach. A confounder in evaluating visual memory using this method is that the individual must be able to draw; otherwise the assessment of visual memory cannot be held as valid.

The Symbol-Digit Paired Associate Learning Task does not require drawing (13). In this task, seven cards, each with an unfamiliar symbol and a single corresponding digit, are shown for 3 sec. Next, the symbol alone is presented as the retrieval cue, and the corresponding digit must be provided by the subject. After the response, the pair is displayed for another 3 sec. Four trials are given. Like the RAVLT, which is used to assess verbal memory, the symbol-digit task yields a learning curve for visual memory.

The Block Design Subtest from the WAIS-R is probably the most widely used measure of visuoconstructional-assembly ability. On this task, red and white blocks must be arranged to correspond to a printed design. There are time limits for each problem and bonus points are given for rapid response time. This test has been shown to be sensitive to the effects of lead (14).

### Executive/Motor Skills

Sustained attention and executive/motor skills have been reported to be affected by solvent exposure. Therefore, in

evaluating hazardous effects of VOCs, this cognitive domain should receive attention. Two tests that are sensitive in detecting not only neurotoxic exposure, but any type of CNS damage, are the Digit-Symbol Substitution Test from the WAIS-R and Trails A and B tests from the Halstead Reitan Neuropsychological Test Battery (15). For the Digit-Symbol test, at the top of a page, a printed key pairs each of the numbers 1 through 9 with a different arbitrary symbol. The remainder of the page contains four rows of randomly ordered numbers. The individual is then required to match by drawing the correct symbol with the corresponding number. The score is the number of squares completed in 90 sec. This task involves several cognitive abilities: visual memory, learning nonverbal associates, sustained attention, speed of visual scanning, and visuomotor speed. In Trails A, a series of numbers must be connected in order, by pencil on paper. In Trails B, the individual must alternately connect consecutive numbers and letters. For example, the individual must connect the number 1 to the letter A, the number 2 to the letter B, and so on.

Simple visual reaction time is another task that has been shown to be affected by neurotoxins. Reaction time can be measured by using either a reaction-time device or a computer. Basically, the subject must press a button using the index finger of the dominant hand when a light signal appears. Reaction time is recorded in milliseconds. Stimuli are randomly presented so that the presentation of the next stimulus cannot be anticipated. When this task is given over 44 or more trials, an index of vigilance and sustained attention is provided.

Manual dexterity and coordination have been shown to deteriorate with exposure to various neurotoxins. The Purdue Pegboard (16,17) assesses manual dexterity. Small pegs must be placed for 30 sec into round holes. Nine trials are given, three for each hand and three for both hands together. Finally, three more trials, referred to as assembly, are given. This involves alternately placing small washers and collars over the pegs after they have been inserted in the holes. Assembly requires sustained attention and ability to coordinate both hands. Finger tapping (15) is a measure of dexterity/simple motor speed. Using a device that records finger taps, a key which resembles a telegraph key must be tapped as rapidly as possible in 10 sec. Although toxic exposures may impair hand-eye coordination and motor speed either directly or because of fatigue, large differences between the dominant and nondominant hand (greater than 5%) should not be seen. Brain damage from most neurotoxins is diffuse, and significantly faster scores on one hand compared to the other may suggest a lateralized dysfunction and would therefore be incongruent with a diagnosis of solvent/VOC neurotoxic exposure.

## Discussion

Currently, neuropsychological assessment is the best method for detecting adverse effects of chemicals on the CNS, although caution must be used in interpreting findings. In order to determine if an individual's score is abnormal, adequate norms must be available to which an individual's scores can be compared. Unfortunately, adequate norms do not currently exist for blue-collar workers, who may, in some instances, be of lower intellectual ability than the normative samples used. If the worker's score is compared to scores of individuals with higher intelligence levels, then a misdiagnosis of having a CNS injury when none exists is likely. However, there have recently been

attempts to develop norms on appropriate worker populations (18) and to develop separate norms based on vocabulary scores (7). In addition to intelligence, neuropsychological tests are also affected by age and sex (7,17,19-21). Therefore, adequate norms examining each of these important variables is necessary to ensure accuracy when making a diagnosis. The effects of these confounding variables on specific neuropsychological tests are presented in Table 2.

Neuropsychological tests have been shown to have high sensitivity but low specificity. When abnormal neuropsychological results are obtained, it must be determined if these abnormal results are due to a neurotoxic effect or to an alternative etiology. Although the patients may report that the development of their cognitive difficulties is recent, in many cases review of school records suggests that these difficulties may be longstanding (subnormal level of intelligence or a longstanding learning disability). In addition, cognitive impairment may be indicative of other diseases of the CNS such as multiple sclerosis, cerebral vascular events, and Alzheimer's disease, and therefore do not reflect neurotoxic effects at all. Depression or anxiety disorders will also negatively affect performance, producing difficulties with attention/concentration, psychomotor speed, dexterity, learning, and memory. Because similar cognitive difficulties are seen with both neurotoxic effects and anxiety/depression, if abnormal test results are found, it is often difficult to determine if these impairments are due to CNS damage produced by a neurotoxin, emotional state of the patient, or an interaction of the two. If inconsistencies in performance are found, such as the patient doing better on a harder task than on an easy task, emotional factors are more likely to be responsible. Both CNS damage and affective disorders produce impaired learning and memory. When specific aspects of memory are examined, recall tends to be impaired and acquisition remains relatively intact with affective

Table 2. The effects of age, sex, and vocabulary on neuropsychological test performance.<sup>a</sup>

Test	Age	Sex	Vocabulary
Serial Digit Learning	***		
Vocabulary	**		
Logical Memory			
Immediate			***
Delayed			***
Verbal-Verbal IV	***	*	
Verbal Fluency (FAS)		*	***
Symbol Digit Learning	***	*	**
Block Design	***	*	*
Digit Symbol	***	*	*
RAVLT V	***	***	
RAVLT Recognition		*	
RAVLT Intrusions		***	
Purdue Dom	***	***	
Purdue N Dom	***	*	
Purdue Both	***		
Purdue Assembly	***	*	
Similarities			***
Trials A	***		
Trials B	***		
Reaction time	***	***	
Truncated mean	***	***	
Minimum	***	***	
Visual reproduction	***		
Consonant trigrams	**	*	***

<sup>a</sup>(\* )  $p < 0.05$ , (\*\* )  $p < 0.01$ , (\*\*\*)  $p < 0.001$ .

disorders. In contrast, with CNS damage, both acquisition and recall will be impaired. Therefore, when interpreting test results, both the level of performance and specific patterns of performance need to be examined.

As with any diagnostic process, the ability to make a differential diagnosis between neurotoxic exposure, neurologic disease, psychiatric disturbance, or malingering is based on the entire evaluation (i.e., history, neurological exam, biological monitoring, nerve conduction studies, EEG, CT/MRI, neuropsychological evaluation).

Repeat testing can be helpful in determining the presence of CNS effects. A correct diagnosis can be aided by showing that some improvement occurs after the patient is removed from the workplace. When a worker is removed from the source of an exposure, symptoms are generally reversible. Therefore, it should be possible to measure improvement in test performance. If performance deteriorates significantly without re-exposure, then the worker could either be suffering from a progressive brain disease or a secondary psychological reaction to the exposure.

Psychiatric disturbances associated with neurotoxic exposure may result directly from the toxic effects on the CNS or indirectly from psychological reactions to occupational exposure, injury, or illness. Psychological reactions to exposure may be as important as the direct effects of the known toxic substances in the etiology and persistence of symptoms. Acute exposure to toxic or potentially toxic substances and the occurrence of symptoms and illness while at work is a frightening occurrence and often sufficiently stressful to cause severe psychological disorders, adjustment disorders, and typical and atypical post-traumatic stress disorders (22,23).

An adverse psychological response to an exposure where there is recovery from the direct toxic effects but the individual continues to experience distressing symptoms may be the result of the interplay of many factors. When the patient finds out that he has suffered an exposure, there is an intense fear of the unknown. The patient as well as his family and friends may view an industrial exposure as more threatening and mysterious than other types of illness. These fears may serve to reinforce the patient to increase his dependency on family and medical personnel. The patient may also interpret exposure as evidence of lack of concern for his safety on the part of the management or company. Supervision, safety, and medical department personnel may be unhappy when their efforts to prevent exposures fail. This may affect their approach to the worker which may be interpreted by the worker as hostility toward him or her. In addition, failure to find elevated blood or urine levels of a specific substance in light of the experience of symptoms may cause the worker to feel even more uncertain and fearful. Sutton (24) suggests that these emotional complications can be prevented by *a*) prompt investigation and correction of the factors responsible for the exposure, *b*) disclosure of the possible adverse health effects associated with the chemical in order to prevent anxiety about fear of the unknown, *c*) showing medical competency that will instill confidence and mutual trust, and *d*) avoidance of animosity by the employer.

In a subgroup of exposed individuals, distressing symptoms may continue to be experienced because these symptoms have been conditioned. This conditioning adheres to a Pavlovian conditioning model in which symptoms are an unconditioned or

naturally occurring response to exposure to an odorous neurotoxic substance. The association of the odor of the toxicant with the symptoms of the exposure causes classical conditioning of the strong odor alone, which can serve in the future as a conditioned stimulus (CS), eliciting the same symptoms as the toxicant itself. Repeated or prolonged exposure strengthens the conditioned association between odor and illness. When generalization of a response occurs, a different odor (CS) will elicit the same response as the original stimulus. The level of intensity of a generalized response is dependent on the degree of similarity between the original stimulus. Symptoms that increase in severity after removal from the source of exposure may be the result of learning, albeit unintentional learning (25).

While these workers tend to report diminution of symptoms when they are in a relatively odor-free environment, a clean odorless environment is, unfortunately, difficult to obtain in the present society. In light of this classical conditioning model, treatment of these individuals could consist of psychotherapy using behavioral techniques such as systematic desensitization to extinguish the conditioned response. Systematic desensitization has been used successfully in treating phobias (26), and there are now a few anecdotal reports of alleviation of symptoms with this technique (22,25).

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